

KINETICS AND MECHANISM OF OXIDATION OF OMEPRAZOLE BY POTASSIUM FERRATE

VIDYAVATI SHASTRY, RAMYASHREE H & RAVINDRA K. S

Department of chemistry, SEA College of Engineering and technology, Bangalore, India

ABSTRACT

The kinetics and mechanism of oxidation of Omeprazole [6-methoxy-2-[(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole] by Potassium ferrate have been studied at 25°C. The stoichiometry has been observed to be 1:1 ratio of Fe(VI) ion and OMZ consumed. First order kinetics with respect to K_2FeO_4 was observed for the oxidation of OMZ. The effect of halide ions, ionic strength and dielectric constant has been studied on the rate of reaction. The reaction products were identified and characterized by LCMS. A suitable mechanism has been proposed on the basis of experimental results.

KEYWORDS: Omeprazole, Potassium Ferrate & Oxidation

Received: Jul 24, 2019; **Accepted:** Aug 14, 2019; **Published:** Oct 25, 2019 **Paper Id.:** IJMPSDEC20192

INTRODUCTION

Omeprazole [6-methoxy-2- [(4-methoxy-3, 5-dimethylpyridin-2-yl) methylsulfinyl]- 1H- benzimidazole [1]. Omeprazole is a medication used in the treat certain stomach and esophagus problems (such as acid reflux, ulcers). It relieves symptoms such as Heart burn, difficulty swallowing and persistent cough. “Omeprazole belongs to a class of drugs known as Proton pump inhibitors (PPIs) and it is derivative of timoprazole that is used in the therapy of stomach ulcer and Zollinger –Ellison syndrome. It works by decreasing the amount of acid your stomach makes. This medication helps heal acid damage to the stomach and esophagus, helps prevent ulcers, and may help prevent cancer of the esophagus. Omeprazole irreversibly blocks the enzyme system on parietal cells that is needed for secretion of gastric acid. It is a specific H^+/K^+ ATPase inhibitor. This is the enzyme needed for the final step in secretion of gastric acid. Omeprazole contains a tricoordinated sulfinyl sulfur in a pyramidal structure and therefore can exist as either the (S)- or (R)-enantiomers. Omeprazole is a race mate, an equal mixture of the two. In the acidic conditions of the canaliculi of parietal cells, both enantiomers are converted to chiral products (sulfenic acid and sulfenamide configurations) which react with acysteine group in H^+/K^+ ATPase, thereby inhibiting the ability of the parietal cells to produce gastric acid”.

Potassium Ferrate is the chemical compound with the formula K_2FeO_4 . This purple salt is paramagnetic, and is a rare example of an iron(VI) compound. In most of its compounds, iron has the oxidation state +2 or +3 (Fe^{2+} or Fe^{3+}). Reflecting its high oxidation state, FeO_4^{2-} is a powerful oxidizing agent. “The iron (VI) derivative, potassium ferrate(VI) has properties such as high stability, oxidizing power, selectivity, and a non-toxic by-product $Fe(III)$, that make the potassium ferrate (VI) an environmentally friendly oxidant for natural waters[2]. Potassium ferrate is a powerful oxidizing agent in the whole pH range, it is widely used as a water treatment agent in 1970s. It can remove the phenolic, sulfide and other organic pollutants which are residual in wastewater and also can oxidize the cyanide into NO_2^- , NO_3^- and HCO_3^- which are harmless to environment. Ferrate as a very effective, selective

oxidant which can remove effectively H_2S , CH_3SH_2 and NH_3 etc odour substances in biological sludge. The treated sludge can be used as chemical fertilizer and soil conditioner, it is propitious to waste resource utilization. Applied prospects of ferrate oxidation are becoming hotspot of research. Oxidability of ferrate is stronger than potassium permanganate, ozone and chlorine. As a new water treatment agent, it has a trend to replace chlorine-atom. In recent years, James Carr etc. used potassium ferrate as water treatment agent, while they studied self-decomposition of potassium ferrate in a wide pH range ($\text{pH}=2.53\text{--}9.31$) and the reaction of oxidizing a variety of organic matters. They had proposed rate equation which is applicable to the majority systems[3]. The rate equation includes self-decomposition of potassium ferrate and the reaction of potassium ferrate with the substrate. They also established new methods to deal with kinetic data of such reaction systems”.

EXPERIMENTAL

Materials and Methods

All chemicals used in this investigations were of Analytical Grade. The substrate pure Omeprazole was purchased from Everest organics limited, Hyderabad, India and was used as received. Solutions were prepared by dissolving requisite amount of OMZ [1.5×10^{-3}] in NaOH and Potassium Ferrate [1.5×10^{-4}] is prepared in distilled water. NaOH [1×10^{-2}], KCl [1×10^{-1}] and were also prepared in doubly distilled water and standardized by standard methods[14].

Preparation of Potassium Ferrate

“Potassium ferrate (K_2FeO_4) of high purity was prepared by the method of Thompson et al[4] using ferric chloride, potassium hydroxide and sodium hypochlorite. Volumetric titration analysis we have used to determine the ferrate concentration accurately. In addition to this, a visible spectroscopy method can be used to measure the ferrate concentration at a wavelength of 508nm[5].



Solution of potassium ferrate was always freshly prepared before experiment”.

Kinetic Methods

Kinetic measurements were carried out using a UV –Vis Spectrophotometer and were performed under the pseudo-first order condition with Omeprazole concentration [1×10^{-3}] greater than potassium ferrate concentration [1.5×10^{-4}] at 25°C . The reaction was initiated by mixing solution of omeprazole [1.5×10^{-3}] and potassium ferrate [1.5×10^{-4}] which contains the required quantities of KCl [1×10^{-1}] and NaOH [1×10^{-2}]. The ferrate shows maximum absorbance at 508nm. The temperature was maintained at 25°C . The first order rate constants calculated from the linear plots of $\log[\text{Fe(VI)}]$ v/s time were reproducible within $\pm 5\%$.

Stoichiometry and Product Analysis

In order to analyse obtained kinetic results, the stoichiometry of Fe(VI) [1.5×10^{-4}] and Omeprazole [1.5×10^{-3}] were determined spectro photometrically. Varying the oxidant Fe(VI) to OMZ were equilibrated at 25°C for 24 hours. Reaction mixture was kept over 24 hours at room temperature and after the completion of reaction excess of potassium ferrate was measured spectro photometrically at 508nm. The stoichiometry of the reaction was found to be 1:1. The product was identified by LC-MS spectra which give M^+H^+ peak at 245.32mHz [Figure 1]. The result indicated that 1 mole of OMZ react with 1 mole Fe(VI). Fe(III) is identified by spot test the reaction with potassium ferrocyanide, with $\text{K}_4\text{Fe(CN)}_6$ it gives reddish brown colour.

The product was found to be [5-(hydroxymethyl)-1-methyl-2-(methyl sulfanyl)-1H-imidazol-4-yl]methyl methyl carbamate.

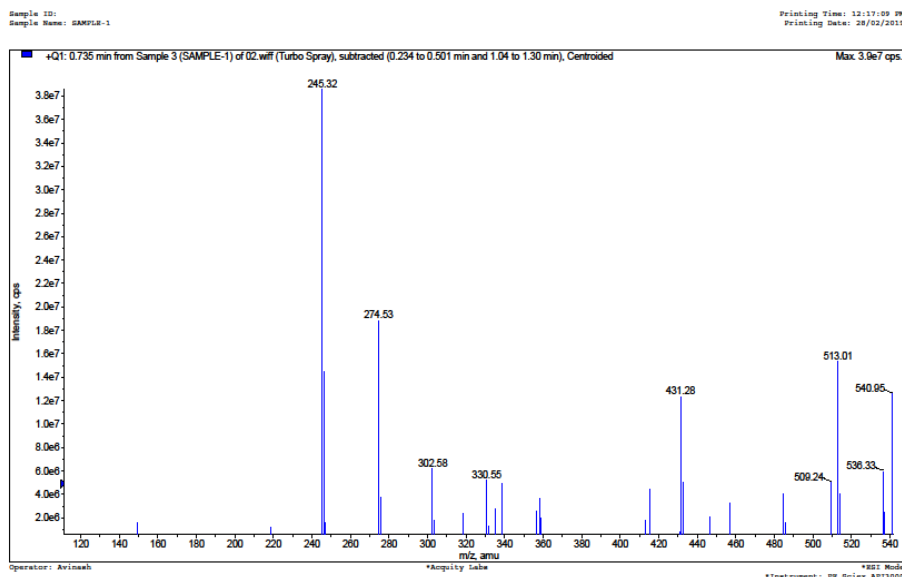


Figure 1: LCMS Spectra of Oxidation of Product of Omeprazole.

RESULTS AND DISCUSSIONS

Effect of Potassium Ferrate

Fe(VI) varied from 0.5×10^{-4} to 4.5×10^{-4} mol dm^{-3} keeping OMZ [1×10^{-3}], NaOH [1×10^{-2}] and KCl [1×10^{-1}] constant. The linear plots obtained by plotting the graph of log absorbance versus time indicates the reaction is first order with respect to ferrate.

Effect of Omeprazole

Effect of Omeprazole was varied its concentration from $[0.5 \times 10^{-3}]$ to $[2.5 \times 10^{-3}]$ keeping potassium ferrate(VI) [1×10^{-4}], NaOH [1×10^{-2}], KCl [1×10^{-1}] at constant.

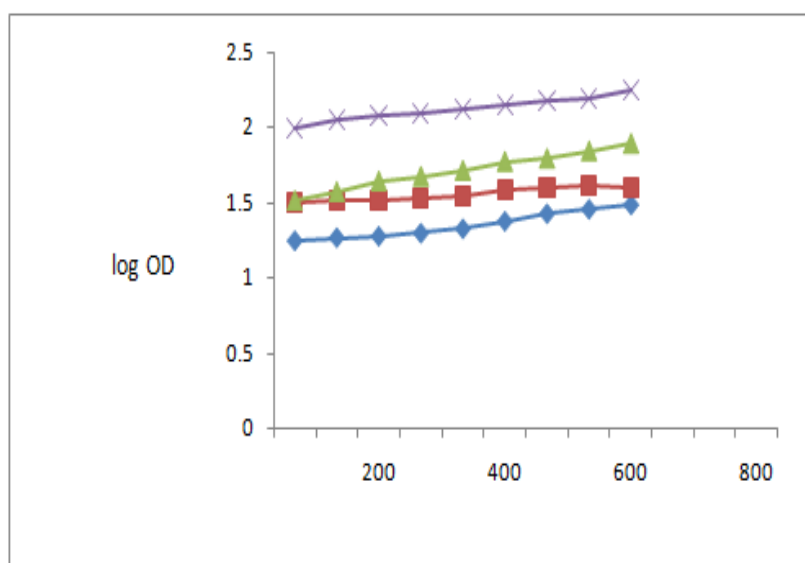


Figure 2: A Graph of Log OD versus Time shows First Order with Respect Omeprazole.

Effect of Sodium Hydroxide

The concentration of NaOH was varied from $0.05 \times 10^{-2} \text{ mol dm}^{-3}$ to $0.3 \times 10^{-2} \text{ mol dm}^{-3}$ by kept all other conditions constant. The rate constant decreased with the increase in [alkali]

Effect of Ionic Strength

At constant concentration of reactants, the ionic strength was varied $[\text{KCl}] \times 10^{-1}$. Ionic strength had negligible effect on the rate of reaction.

Effect of Dielectric Constant

The dielectric constant was studied by the addition of methanol to the reaction medium but it was negligible effect on the rate of reaction.

Effect of pH on OMZ Oxidation

“Similar experiments were conducted to determine the values of k_{app} at different pH levels. pH dependence was also observed with the oxidation of carbamazepine, nonylphenol, by Fe(VI)[6]. The pH dependence of the rate constant might be attributed to the speciations of both OMZ and Fe(VI). Chemically, due to the p_{ka} value of omeprazole and Fe(VI), OMZ forms major form of solution, whereas two species of Fe(VI) (ie., HFeO_4^- and FeO_4^{2-}) [7] may be observed under experimental pH conditions $7.0 \leq \text{pH} \leq 12.0$ ”.

Effect of Halide Ions

The addition of Halide ions that is NaCl had no effect on the rate of oxidation of Omeprazole

Test for Free Radical

The addition of aqueous acrylamide solution to mixture of omeprazole and potassium ferrate in the presence of NaOH, showed no generation of free radicals.

Effect of Added Product

Aldehyde, Ammonia was added, but did not show any effect on the rate of the reaction.

Effect of Temperature

The effect of temperature was also studied at different temperature like 298,302,308,312K at fixed concentration of omeprazole [1.5×10^{-3}] and potassium ferrate(VI) [1.5×10^{-4}], NaOH [1×10^{-2}], KCl [1×10^{-1}] were at constant condition. Rate of reaction increased with increase in temperature. The rate constant 'k' is at different temperature.

From linear Arrhenius plots of $\log k$ v/s $1/T$, the activation parameters ΔH^\ddagger , ΔS^\ddagger were calculated and tabulated in Table 2. Rate k is calculated at different temperature and is given in the Table 1.

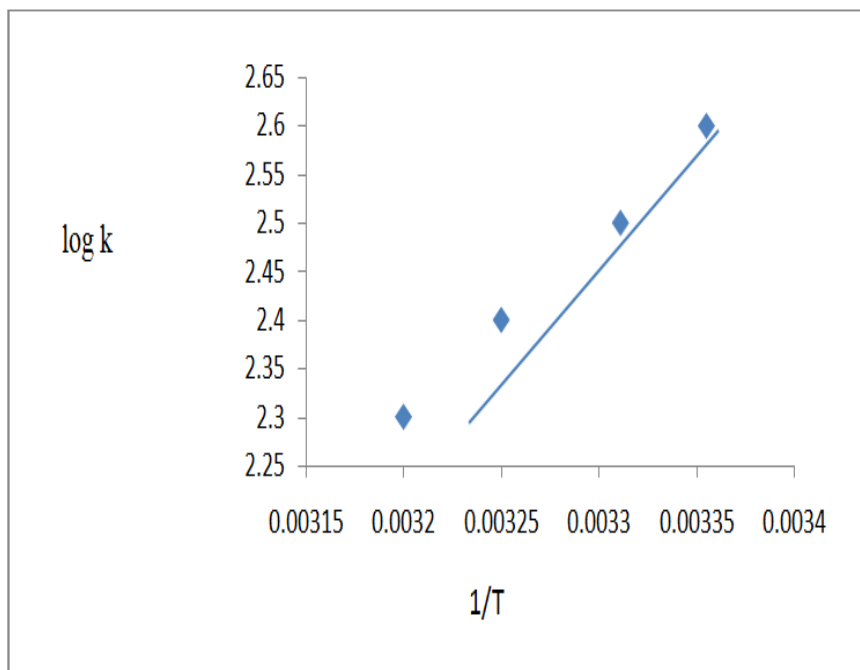


Figure 3: Arrhenius Plot of Log k v/s 1/T at Different Temperature.

Table 1: Rate Constant with Respect to Temperature

Temperature	K _{obs}
298	2.5
302	3.0
307	3.9
312	5.2

Table 2: Activation Quantities

Parameters	Values
E _a	34.3
ΔH [#]	11.603
ΔG [#]	2208.41
ΔS [#]	-7.501

The oxidation of ferrate was dependent on temperature since the k_{app} of OMZ destruction by ferrate was gradually increased with elevated temperature from 5° C to 35°C[8].

Since according to the Arrhenius equation,

$$\ln k_{app} = \ln A - \frac{E_a}{RT}$$

Where, E_a is the apparent activation energy, R is the universal gas constant,

A is the Arrhenius constant. In this experiment E_a was determined to be 34.3 kJmol⁻¹, enthalpy(ΔH) and entropy(ΔS) can also determined to be 11.60±0.5 and -7.5 J/k/mol⁻¹ respectively. From the literature survey, the activation parameter for the reaction of carbamazepine[9], same as that OMZ oxidation by Fe(VI) has been conducted. E_a and ΔH values indicated sensitive energy difference between transition state and the reactant[10]. Since in the relative lower effect of temperature on the reaction between Fe(VI) and OMZ”.

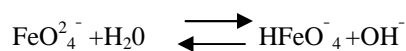
Table 3: Effect of Varying Concentration of OMZ [1X10-3], Fe(VI) [1X10-4], NaOH [1X10-3], KCl[1X10-1] on the Rate of the Reaction at 25°C

[Fe(VI)]X10 ⁻⁴ (moldm ⁻³)	[OMZ]X10 ⁻³ (moldm ⁻³)	[OH ⁻]X10 ⁻² (moldm ⁻³)	KClx10 ⁻¹ (moldm ⁻³)	KobsX10 ⁻³ (moldm ⁻³)	KcalX10 ⁻³ (moldm ⁻³)
0.5	1.5	0.1	1.0	2.5	3.16
1	1.5	0.1	1.0	2.6	3.16
1.5	1.5	0.1	1.0	2.5	3.16
2	1.5	0.1	1.0	2.5	3.16
2.5	1.5	0.1	1.0	2.6	3.16
1.5	0.5	0.1	1.0	1.1	1.05
1.5	1	0.1	1.0	2.0	2.08
1.5	1.5	0.1	1.0	2.5	3.16
1.5	2.0	0.1	1.0	2.9	4.21
1.5	2.5	0.1	1.0	3.2	5.27
1.5	1.5	0.05	1.0	3.5	3.87
1.5	1.5	0.1	1.0	2.5	3.16
1.5	1.5	0.2	1.0	1.6	2.31
1.5	1.5	0.3	1.0	1.5	1.82
1.5	1.5	0.1	0.5	2.4	3.16
1.5	1.5	0.1	1.0	2.5	3.16
1.5	1.5	0.1	1.5	2.5	3.16
1.5	1.5	0.1	2.0	2.5	3.16

From the experimental result, scheme of reaction is given as below



In this experiment, FeO^{2-}_4 undergoes partial hydrolysis



Thus,

$$K_h = \frac{[\text{HFeO}^-_4][\text{OH}^-]}{[\text{FeO}^{2-}_4]}$$

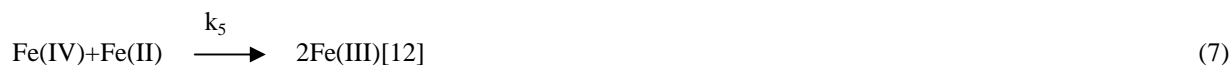
$$k_h = K_w/Ka_2 = 6.31 \times 10^{-7}$$

In this experiment is performed at pH 12

$$\frac{[\text{HFeO}^-_4]}{[\text{FeO}^{2-}_4]} = \frac{K_h}{[\text{OH}^-]} = 3.9 \times 10^{-2} [11]$$

From above discussion, We can propose mechanism





Where R is Reductant

Since the reaction shows that rate of consumption of $[\text{FeO}_4^{2-}]$, then the expression was derived as follows:

$$-\frac{d[\text{FeO}_4^{2-}]}{dt} = k_2[\text{HFeO}_4^-][\text{R}] - k_{-2}[\text{X}] \quad (8)$$

From (4) & (5), [X] can be obtained by the approximation steady processing method

$$[\text{X}] = \frac{k_2[\text{HFeO}_4^-][\text{R}]}{k_{-2} + k_3[\text{OH}^-]} \quad (9)$$

A comparison of equation 4 with 2 imparts:

$$-\frac{d[\text{FeO}_4^{2-}]}{Dt} = \frac{k_2 k_3 K_h [\text{FeO}_4^{2-}][\text{R}]}{k_{-2} + k_3[\text{OH}^-]} \quad (10)$$

$$= \frac{k_2 k_3 K_h [\text{R}]}{k_{-2} + k_3[\text{OH}^-]} [\text{FeO}_4^{2-}]$$

From (3) we can written as

$$[\text{HFeO}_4^-] = \frac{K_h [\text{FeO}_4^{2-}]}{[\text{OH}^-]} \quad (11)$$

A comparison of equation equation 11 and 10, we get equation 12

$$[\text{HFeO}_4^-] = \frac{k_2 k_3 K_h [\text{R}]}{k_{-2} + k_3[\text{OH}^-]} \quad (12)$$

$$\text{So, } k_{\text{obs}} = \frac{k_2 k_3 K_h [\text{R}]}{k_{-2} + k_3[\text{OH}^-]} = \frac{k_2 k_3 K_h [\text{R}]}{1 + k'[\text{OH}^-]} \quad (13)$$

$$\text{Here, } k' = \frac{k_3}{k_{-2}}$$

Taking the reciprocal of the equation (12) we have

$$\frac{1}{k_{\text{obs}}} = \frac{1 + k'[\text{OH}^-]}{k_2 k' K_h [\text{R}]} = \frac{1}{k_2 k' K_h [\text{R}]} + \frac{[\text{OH}^-]}{k_2 K_h [\text{R}]} \quad (14)$$

The equations indicate that the reaction should be first order both with Fe(VI) and reductant. The plot of $1/k_{\text{obs}}$ versus $[\text{OH}^-]$ derives from equation (13) at constant [R] is linear with positive intercept. From this equation, the plot of $1/K_{\text{obs}}$ versus $1/[\text{OMZ}]$ is linear. From this linear plots k_2 k' are calculated and values are found to be 9090.9 and 11627 respectively. Substituting the values of k_2 and k' in the rate equation, the rate constants were calculated. Using these constants, the rate constants were calculated over different experimental conditions". The k observed and k calculated values are in good agreement as shown in table 3.

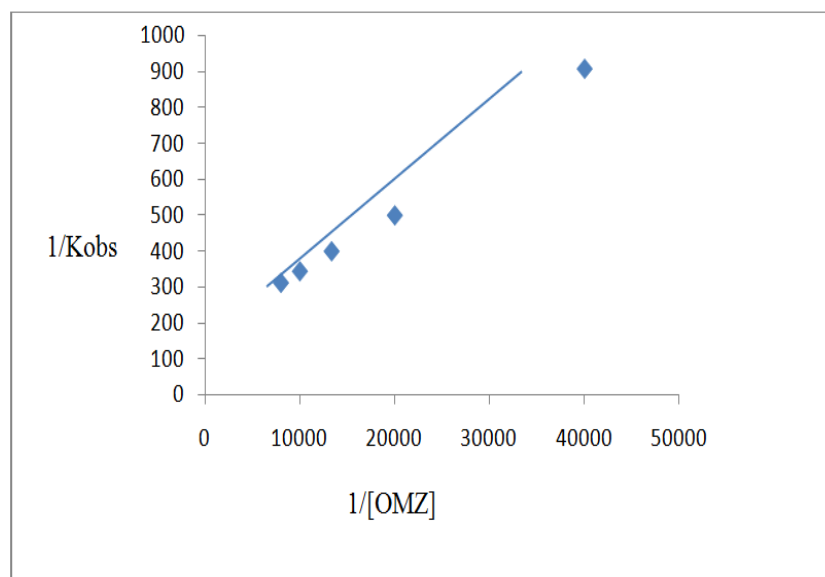


Figure 4: Plot of 1/k_{obs} Versus 1/[OMZ] for the Verification of Rate Law at [OMZ]=1X10⁻³

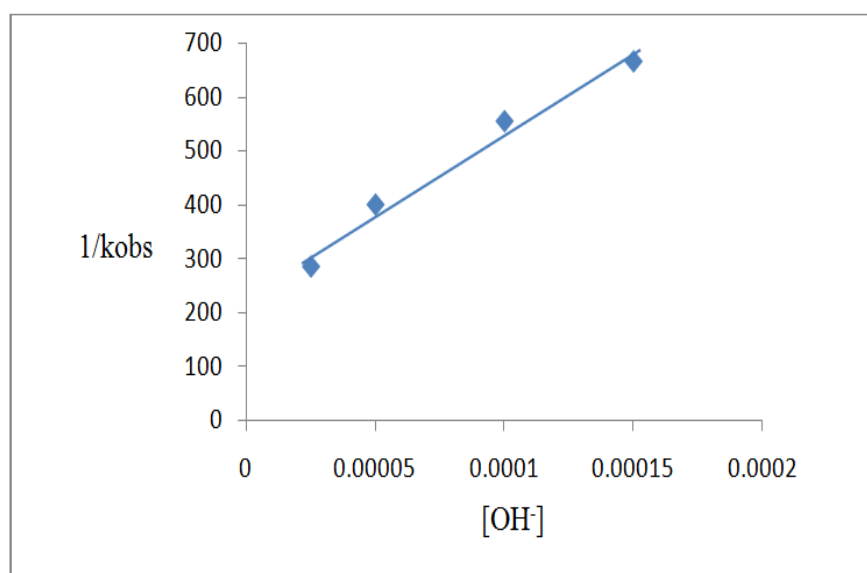


Figure 5: Plot of 1/k_{obs} Versus [OH⁻] for the Verification of Rate Law at [OMZ]=1X10⁻³, [Ferrate(VI)]=1X10⁻⁴, [NaOH]=1.0X10⁻² mol dm⁻³, KCl=1X10⁻¹ mol dm⁻³.

CONCLUSIONS

Kinetics and oxidation of Omeprazole by Potassium ferrate in alkaline medium has been studied at 25°C. The stoichiometry of oxidation Omeprazole and ferrate is found to be 1:1. The oxidation product was found to be [5-(hydroxymethyl)-1-methyl-2-(methyl sulfanyl)-1H-imidazol-4-yl]methyl methyl carbamate. There is no salt effect that means no reaction of the ions and no free radical formation in the reaction. The arrhenius plot shows how activation energy and temperature affect the sensitivity of the reaction rate.

ACKNOWLEDGEMENT

We are thankful to SEA College of Engineering and technology, Bangalore for providing the laboratory facilities to bring about this work. And thanks for Everest organics limited, Hyderabad, India for providing drug sample

REFERENCES

1. SShashidhar, Vidyavathishastri and B C Sateesh, *International journal of pharmacy and pharmaceutical research.*,13, 59 (2018).
2. Virender K. Sharma, *Advances in Environmental research.*,6,143 (2002).
3. Shan Jinhuan and Zhang Jiying, *E-Journal of chemistry.*,8,903 (2011).
4. G. W. Thompson, L. T. Ockerman and J. M. Schreyer, *J. Am. Chem. soc.*,73, 1379(1951).
5. R. J. Audette, J. W. Quail, P. J. Smith, *Tetrahedron Lett.*,3, 279 (1971).
6. Mustafa, M., Iftikhar, M., Munaidy, R. K., & Shah, M. J. (2015). Role of *Helicobacter pylori* infection in peptic ulcer disease. *International Journal of Research in Applied, Natural and Social Sciences*, 3(8), 29-38.
7. Yingling wang, Haijin Liu, Guoguang Liu, YouhaiXie, ShuyanGao., *Science of the Total Environment.*, 506-507, 252(2015).
8. Jihuan shah, Jiying Zhang, Haixiashan, Xioqianwang, *International journal of chemistry.*,2, 2(2010).
9. Patil, P. M., & Kannapurkar, S. S. (2016). Development and validation of UV-Spectrophotometric method for simultaneous determination of atazanvir sulphate and ritonavir in its pure and pharmaceutical dosage forms. *IJMPS*, 6(1), 79-86.
10. Virender K. Sharma, *Coordination chemistry review.*, 257, 495 (2013).

AUTHOR'S PROFILE

Dr Vidyavati Shastry professor and HOD Department of chemistry, SEA College of engineering and technology, Bangalore. Obtained her Msc and Ph.D from Karnataka university, Dharwad. She has more than 30years experience in teaching field. She is guiding 6 research students. Three students obtained their Ph.D degree from Visvesvaraya technological university, belgaum. She has published about 35 papers in international journals. She is editor of International journals and got membership of ISTE & Indian congress association.

Ramyashree H, Research scholar in SEA College of engineering and technology, Bangalore. Her Bsc and Msc are from Davangere university, Karnataka. Her research is in process

Ravindra K.S Assistant professor, Department of chemistry, SEA College of engineering and technology, Bangalore. He completed his Bsc., and Msc., in kuvempu university, shimoga Karnataka. He has 8 years experience in teaching. He is also partime research scholar in SEA college of engineering and technology.

